

Introduction

Proactive strategies to avoid infectious disease

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Infectious disease exerts a large selective pressure on all organisms. One response to this has been for animals to evolve energetically costly immune systems to counter infection, while another—the focus of this theme issue—has been the evolution of proactive strategies primarily to avoid infection. These strategies can be grouped into three types, all of which demonstrate varying levels of interaction with the immune system. The first concerns maternal strategies that function to promote the immunocompetence of their offspring. The second type of strategy influences mate selection, guiding the selection of a healthy mate and one who differs maximally from the self in their complement of antigen-coding genes. The third strategy involves two classes of behaviour. One relates to the capacity of the organisms to learn associations between cues indicative of pathogen threat and immune responses. The other relates to prevention and even treatment of infection through behaviours such as avoidance, grooming, quarantine, medicine and care of the sick. In humans, disease avoidance is based upon cognition and especially the emotion of disgust. Human disease avoidance is not without its costs. There is a propensity to reject healthy individuals who *just* appear sick—stigmatization—and the system may malfunction, resulting in various forms of psychopathology. Pathogen threat also appears to have been a highly significant and unrecognized force in shaping human culture so as to minimize infection threats. This cultural shaping process—moralization—can be co-opted to promote human health.

Keywords: psychoneuroimmunology; mate selection; disgust; hygiene; stigma; cultural evolution

The most recent World Health Organization data indicate that around a quarter of all deaths result from infectious disease [1]. Yet, prior to advances in sanitation and hygiene in the nineteenth century and medicine in the twentieth century, mortality rates due to infectious disease were considerably higher [2]. Infectious disease is a powerful selective force and humans, along with other animals, have evolved energetically costly immune systems to deal with pathogen threats. In humans, the immune system (considering just leucocytes) uses around 1600 kJ per day, and when stimulated by pathogens energy demands increase significantly, raising basal metabolic rate between 9 and 30 per cent or more (e.g. 50% in the case of sepsis) [3]. Not surprisingly, there is likely to be a considerable adaptive value in evolving systems that reduce the likelihood of becoming infected, thus avoiding the risk and energy costs of fighting an infection. Moreover, the presence of such proactive systems allows animals—including humans—to direct resources to reproduction rather than to the immune system. These disease avoidance systems are the focus of this theme issue.

Disease avoidance in humans and animals can be categorized into three different types, all of which involve varying levels of interaction with the immune system. The closest level of interaction occurs with transgenerational immune priming [4]. Here, maternal exposure to a pathogen promotes immunocompetence in her offspring in at least three ways: (i) by the direct transfer of antibodies or immunoglobulins from mother to offspring; (ii) by alterations in maternal reproductive behaviour (e.g. gender skewing if females are more likely to survive); and (iii) by epigenetic changes. Whether such strategies occur in humans has yet to be established, but evidence is certainly accruing in animals. The most recent developments concern epigenetic changes, which appear to prepare the progeny for a particular life history—in this case one characterized by a ‘disease-rich’ environment. Emerging data in mice seem to suggest that maternal exposure to disease cues lead to changes in their progenies’ behaviour. Specifically, there is greater investment in the immune system at the cost of less aggressive behaviour, and by implication, less access to sexual resources. In the current issue, Curno *et al.* [5] examine the effects of maternal infection with *Babesia microti* before pregnancy on the immunocompetence and behaviour of the offspring.

The second type of disease avoidance concerns mate choice. Selecting a mate involves a number of decisions that are influenced by short- and long-term

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One contribution of 11 to a Theme Issue ‘Disease avoidance: from animals to culture’.

considerations about disease. In the short term, a sick mate may infect their sexual partner with a pathogen, incurring immediate costs in terms of sickness, or more delayed costs such as reduced fertility or chronic illness, as with certain sexually transmitted diseases. A potential mate's current health status may also be predictive of their likelihood of bearing an equal burden of the costs associated with parenting, although this will clearly depend upon the reproductive strategy of the animal in question. A further consideration, and one especially important for the immunocompetence of the offspring, relies on selecting a mate with a non-complementary set of immune genes (human leucocyte antigens (HLA) in humans and major histocompatibility complex (MHC) in other mammals). Humans seem to prefer selecting prospective mates with non-complementary sets of HLA genes; in other words care is taken to avoid incest [6]. These various mate-related disease avoidance strategies, and their costs and benefits, are examined in the article by Tybur & Gangestad [7].

The third type of disease avoidance system concerns behavioural responses which occur either following infection or when a disease-related sign is perceived. When a person or animal becomes sick, they exhibit a range of physiological changes and behaviours designed to minimize energy expenditure so that resources can preferentially be directed to the immune system [3]. Not only then does the person or animal become somnolent, with reduced appetite and hyperthermia, there may also be associative learning between cues that signalled illness onset—especially gastrointestinal cues such as flavour—and the immune- and affect-related systems [8]. Future exposure to such external cues seems to activate avoidance and the immune system, thus acting to minimize future episodes of illness. The neural basis and nature of immune conditioning and sickness-related behaviours are examined in the article by Pacheco-Lopez & Bermudez-Rattoni [9].

Animals and humans also have a repertoire of behaviours that are clearly proactive and which enable them to minimize the risk of contracting an infection [10,11]. Hart [12] describes in this issue the close parallels between animal disease avoidance and the 'pillars' of modern medicine. Animals, from across all phyla, demonstrate various types of disease avoidant behaviour that can be broadly classified into five different strategies: (i) avoidance of disease-related signs and active removal of parasites; (ii) quarantine or peripheralization of new conspecifics; (iii) herbal medicine 'animal style'; (iv) potentiation of immune function by controlled exposure to pathogens; and (v) care of sick or injured group members. Humans demonstrate most of these same behaviours, although their instantiation is far more elaborate than in animals. Indeed, Schaller [13] in this issue suggests that humans have a 'behavioural immune system' comprising emotional, cognitive and behavioural responses to disease threats. A central component of the behavioural immune system is the emotion of disgust [11,14]. A disgust-like response is present in many species (certainly most mammals), and functions to rid the mouth of noxious tasting substances (notably probable poisons—bitter tasting foods [15]). In humans this emotion seems to have been co-opted into a disease avoidance role. As Siegel *et al.* [16] describe in this

issue, humans seem to learn to respond to disease-relevant cues (i.e. faeces, body products, gore, etc.) with disgust. This is acquired via parent–child transmission alongside specific knowledge relating to disease, contamination and germ theory. Once acquired, disgust reactions provide a potent emotional force to avoid cues signalling disease.

While disease avoidance serves functional ends, humans, and probably animals too, seem disposed to infer even innocent cues as *possible* signs of disease (e.g. a chocolate brownie shaped to look like faeces is highly undesirable even though one may know that it is only a chocolate brownie [17]). This propensity can be most readily seen in the stigmatization of people with facial abnormalities wrought by injury or non-infectious illnesses such as psoriasis, eczema or acne [18]. This propensity to avoid individuals who bear *apparent* signs of disease has led several authors to suggest that it offers a powerful explanation for many types of stigmatization as Oaten *et al.* outline here [19].

Although a propensity for false alarms may be adaptive, if potentially costly in terms of lost opportunities for social and sexual interactions, the disease avoidance system more generally, and disgust in particular, may malfunction and contribute to several forms of psychopathology [20]. Davey here [21] outlines the disorders in which contemporary thinking suggests that a dysfunctional disease avoidance system, especially disgust, play a role. These include obsessive–compulsive disorder (contamination forms), blood injury injection phobia and small animal phobias. The emotion of disgust may also be a contributory factor to psychopathologies such as eating disorders, post-traumatic stress disorder, sexual dysfunctions, hypochondrias, height phobia, claustrophobia, separation anxiety, agoraphobia and schizophrenia, which do not seem—at first—so obviously related to disgust.

Disease burden varies considerably both between nation states and within them [22]. Some communities have experienced historically high rates of infectious disease and this seems to have produced systematic cultural adaptations in the form of more collectivist societies [23]. Such societies exhibit greater levels of xenophobia, neophobia, ethnocentrism, reduced dispersal, as well as more constrained and restrictive sexual practices and mores. Indeed, evidence is emerging that infectious disease burden, both historical and current, can be a powerful explanatory variable in explaining differences between cultures [23,24]. As Thornhill & Fincher reveal here [25], current disease burden across the USA accounts for more variance in intimate partner violence, homicide and child maltreatment, than more traditional explanatory variables (e.g. poverty). Disease burden may be a powerful and relatively unrecognized force in human cultural evolution.

A further recent trend has been to study how the process of disease avoidance can be positively co-opted to promote human health and well being. This process which has been termed 'moralization' may underpin the emergence of disease-related cultural effects of the sort described above. Historically, emotions such as disgust and fear have been co-opted for broader goals—such as promoting bodily hygiene and the use of soap in the early twentieth century [2], for campaigns

against smoking, and more recently against fatty and sweet foods [26]. Unfortunately, this process of moralization, which involves yoking the emotion of disgust to particular behaviours or groups of individuals (e.g. smokers), has also been used for malicious political ends by labelling particular ethnic groups as lice or vermin, for example [19]. The use of moralization via disgust to change behaviour is also emerging as a useful tool to promote hand washing. As Curtis [27] describes in the final article of this theme issue, diarrhoeal disease is responsible annually for 1.5 million child deaths, deaths that may be readily avoided with effective hand hygiene, promoted by co-opting disgust.

The growing body of knowledge about disease avoidance, its neural basis and its interactions with the immune system, offer a range of potentially important applications, of which hand hygiene is just one. As described above, disease avoidance may lead to new insights into stigmatization [19], racial vilification, mental health [21], interpersonal violence and conflict [25]. It may also improve our understanding of risky sexual choices and promiscuity [7] through identifying the apparent failures of disease avoidance in sexual decision-making [28]. All of these applied aspects of disease avoidance rest upon advances made in basic science. Nonetheless, the multidisciplinary nature of the field, reflected in this special issue, has been a hindrance to growth because of the often compartmentalized nature of scientific publication. Hopefully, this special issue should serve to introduce readers to all its aspects and to the broad and often unanticipated consequences of disease avoidance.

The authors would like to thank all of the individuals who served as reviewers for the articles in this theme issue and the Australian Research Council for their continued support.

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